Can Immunomodulatory Molecules Work Topically for Psoriasis?

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The potential for new approaches to the topical therapy of psoriasis has made another major step with the report by Rappersberger *et al* about an immunosuppressive molecule that appears to be effective when administered topically. Since the serendipitous observation that the immunosuppressive drug, cyclosporin A (CSA), effectively cleared psoriasis after systemic administration, an aggressive search has been pursued for ways to topically use this drug or a similarly functioning molecule. Topical CSA was shown to block experimental allergic contact dermatitis reactions in animal skin models, possibly by easier penetration into that skin (1). Numerous topical CSA preparations have failed in man, however, despite efforts to improve penetration of the large CSA molecule (molecular weight = 1203) (2). Alternatively, the mechanisms of CSA action may be somewhat different from other presumably similar immunomodulatory drugs. When relatively large doses of painful intralesional injections provided only partial lesional clearing (at high doses) (3), it raised the question of whether CSA works by a local effect in the skin or a systemic interaction on target cells. A similar question has befuddled the potential use of topical methotrexate (4).

In the current report a new macrolide of the ascomycin type (SDZ 281–240) has immunosuppresive actions similar to FK 506 (Tacrolimus), a drug reported as systemically efficacious in psoriasis (5). Rappersberger *et al* believe, with only limited information in this study, that the molecule may have similar mechanisms of action to CSA. The major action would be to block the activation of T-cells by a "psoriasis antigen(s)," thereby suppressing the production of lymphokines, particularly IL-2. These lymphokines appear to induce the hyperplasia of psoriatic keratinocytes leading to the clinical lesions of psoriasis. An *in vitro* experiment in this study supports this hypothesis by showing that stimulated lymphocytes in mixed lymphocyte reactions are blocked from proliferation at extremely low concentrations of the drug (1.2 nM SDZ281–240) while HaCaT, a transformed human keratinocyte cell line, requires 10,000 fold more drug to inhibit proliferation. The authors thus conclude that the drug's effect on eventually stopping the keratinocyte hyperplasia comes by selectively blocking T-cell proliferation rather than a direct inhibition of keratinocytes.

The clinical trial in psoriasis with application of SDZ 281–240 to small plaques shows dramatic improvement of lesions by two concentrations of drug, 1% and 0.1%, as well as a superpotent topical steroid, in comparison to minimal placebo effects. After 10 days of therapy, all active preparations decreased the mean clinical score of 3.0 to less than 0.5. In a variety of histopathological and immunomorphological assays of pre- and post-treatment biopsies, many similar observations were made to those following systemic administration of CSA. Interestingly, most of the immunomorphological parameters were also similar between the SDZ drug and the topical steroid therapy sites. Since many of these observations may reflect just the end result of improvement rather than the primary mechanistic pathway(s), further studies will be needed to pinpoint the biochemical sites of action. The similarity of changes with both the study drug as an "immunosuppressive agent" and the steroid as an "antiinflammatory agent," and both as "antiproliferatives," should lead to many interesting concepts on how to tie this troika of actions together. The mode of action of SDZ281–240 as summarized by the authors would be a downregulation of activated T-cells, decreasing the cytokine-mediated proliferation of keratinocytes that causes the psoriatic epidermis to return to a normal proliferative and differentiated state with clinically clear skin.

For the psoriatic patient population, the great majority of whom have limited disease and use topical medications, a new and potentially highly effective topical therapy would be a very welcome addition to the recent availability of calcipotriene and the probability of a topical retinoid, tazarotene, in the forseeable future. Many basic and clinical trials need to be done to ascertain the value of this drug including: the therapeutic index (benefit vs risk ratio); the optimal concentration (both concentrations used in this study were approximately equal in effect); potential of significant side effects, both topical and systemic; and importantly, the duration of effectiveness for long term maintainance without the concern of tachyphylaxis. This drug appears to be the first of a new generation of immunomodulating compounds that have the capability of altering the phenotype of psoriasis at the local level. Similarly, the drug may also be active at the local site of other inflammatory diseases, cutaneous, joint and elsewhere.

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